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Treated for Breast Cancer

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<b>13. ABSTRACT (Maximum 200 Words)</b>  <b>Purpose:</b> To determine the incidence, dose/time-dependence, and functional significance of regional cardiac perfusion abnormalities in patients with left-sided breast cancer treated with radiation therapy (RT) with and without doxorubicin. <b>Methods:</b> 126 patients underwent pre-RT single photon emission computed tomography (SPECT) cardiac perfusion imaging. Post-RT images were obtained in 97, 69, 42, 30, 13 and 8 patients 6, 12, 18, 24, 36 and 48 months post-RT. SPECT perfusion images were registered onto 3-dimensional (3D) RT dose distributions. The volume of heart in the RT field was quantified and the regional RT dose was calculated. Changes in regional and global cardiac function were assessed. <b>Results:</b> Overall, 30% of patients developed dose-dependent RT-induced perfusion defects. The incidence of defects increased with the volumes of heart irradiated, and maybe more prevalent in African Americans (vs. Caucasians) and with chemotherapy (vs. RT alone). Perfusion defects were associated with changes in regional wall motion 20-40% of the time and possibly with the development of chest-pain. <b>Conclusions:</b> RT causes dose-dependent cardiac perfusion defects 6-24 months post-RT that appears to be associated with functional changes. The use of chemotherapy and African American race may increase this rate. Long-term follow-up is needed to assess whether these perfusion changes are transient or permanent and to determine if these findings are associated with changes in overall cardiac function and clinical outcome.				
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**INTRODUCTION:**

With the increasing use of radiotherapy in the management of primary breast cancer, there has been rising concern about long-term side effects of radiation therapy (RT). Some randomized series evaluating patients irradiated post-mastectomy report an excess number of cardiovascular deaths in the irradiated group. Additionally, radiotherapy to the heart in conjunction with the chemotherapy drug doxorubicin (Dox) appears to increase the risk of developing cardiac damage. New three-dimensional (3D) RT planning software permit us to calculate the 3D radiation dose distribution in any tissue. Doses can be calculated for complex field arrangements and differences in tissue density may be considered. Single-photon emission computed tomography (SPECT) cardiac perfusion imaging provides a noninvasive assessment of myocardial perfusion and function. Advances in image registration allow us to superimpose the 3D dose distribution onto noninvasive nuclear medicine 3D cardiac imaging studies. Using 3D treatment planning tools and nuclear medicine perfusion imaging of the heart, we attempted to determine the volume of left-ventricle in the RT treatment field, and correlate regions of post-RT perfusion changes with both the RT dose and the use of Dox-based chemotherapy.

**BODY:****Data Presentation, Research Results:****Task 1: Subject recruitment, Data Collection and Analyses, Months 1-12****a. Enroll 15 new African American (AA) patients onto study, obtain baseline scans.**

Between 3/24/03 and 6/16/03 we have enrolled 13 new patients on the study, of whom 5 were AA. Baseline SPECT scans have been obtained on all of these patients.

**b. Register SPECT and treatment planning CT scans.**

All baseline and follow-up SPECT scans performed within the last year have been registered with the treatment planning CT scans.

**c. Perform 3D dose calculations on new patients.**

3D dose calculations have been performed on all new patients entered into the study within the past year.

**d. Obtain follow-up scans on patients from prior study period, and on new AA patients.**

A total of 36 follow-up scans have been obtained over the last year on the 114 patients previously entered into the study. There were six 12-month scans, five 18-month scans, five 24-month scans, ten 36-month scans, and

ten 48-month scans. No patient has reached the 60-month follow-up end point yet. The 12 new patients enrolled on the study over the last year have all been enrolled within the last 6 months; therefore none of them have undergone a 6-month scan yet.

- e. At each follow-up point, the new SPECT scan will be compared to previous scans and data will be reanalyzed with respect to dose distribution and cardiac function. Findings to be entered into patient profile database and stored for analyses.**

The results of all follow-up SPECT scans performed in the last year have been entered into the patient profile database, where they are stored for future analyses.

- f. Relevant clinical follow-up information obtained and recorded on all patients and entered onto data sheets and database.**

Datasheets have been filled out for each follow-up visit that has occurred over the last year and the data contained on these sheets entered into the database.

- g. With a larger number of patients now evaluable for 3-year follow-up, assess for:**

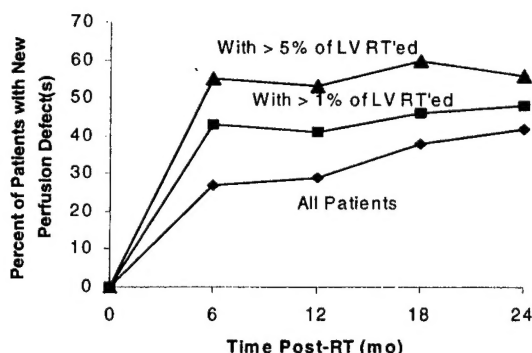
**1) persistence of perfusion changes**

The rates of cardiac perfusion defects at 6-36 months post-RT for patients analyzed as of June 1, 2003 are shown in **Table 1**. As **Table 1** shows, the previously noted defects in the 6-24 month period appear to be persistent at later time points. We will continue to follow these patients to assess the longevity and persistence of these defects.

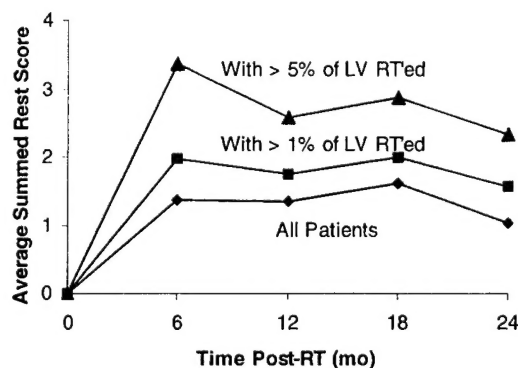
**Table 1: Rates of patients developing new perfusion defect**

Month	New Defect	Subsequent Scan Normal	Subsequent Scan Abnormal	No Subsequent Scan Yet
6	21/77	7/21	13/21	1/21
12	16/55	2/16	11/16	3/16/
18	13/34	1/13	7/13	5/13
24	11/26	1/11	2/11	8/11
36	3/7			

We have previously shown that the incidence of new perfusion defects is highly correlated with the volume of LV included within the radiation field and that these defects persist for the duration of the observation period. With additional FU these conclusions remain valid. **Figure 1** shows this relationship graphically using data analyzed as of June 1, 2003.

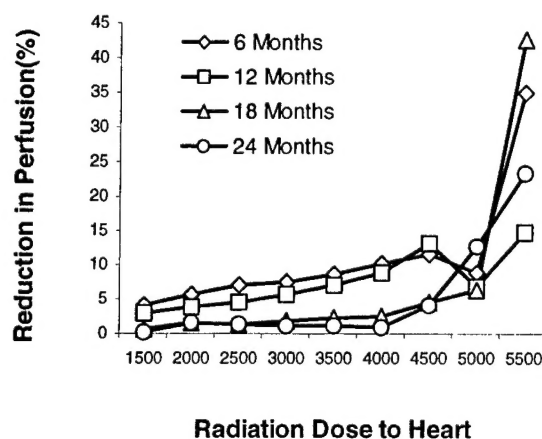


We have also previously demonstrated that the average summed rest score (SRS) increases as the percentage of LV irradiated increases and that the SRS score remains elevated throughout the observation period. With additional FU these findings have not changed. **Figure 2** shows this relationship graphically using data analyzed as of June 1, 2003.



In the Clinical Bridge Award application we showed that decline in cardiac perfusion within any region of the heart (as measured on a SPECT scan) can be related to the dose of radiation received by that region of the heart. By merging a patient's SPECT scan with the 3D dose distribution using image fusion software, changes in regional perfusion can be correlated with regional dose to generate a "patient-specific" dose response curve (DRC). The DRCs of a group of patients can then be summed to generate a "population" DRC. In the Bridge Award we showed the population DRC based on SPECT scans performed 6 months after RT. Over the last year we calculated the population dose response

curves at 6, 12, 18, and 24 months in a cohort of 13 patients (**Figure 3**). These results were presented at the 25<sup>th</sup> Annual San Antonio Breast Cancer Symposium (December, 2002). We will continue to scan patients to further clarify the dose response curve of RT-induced cardiac perfusion defects.



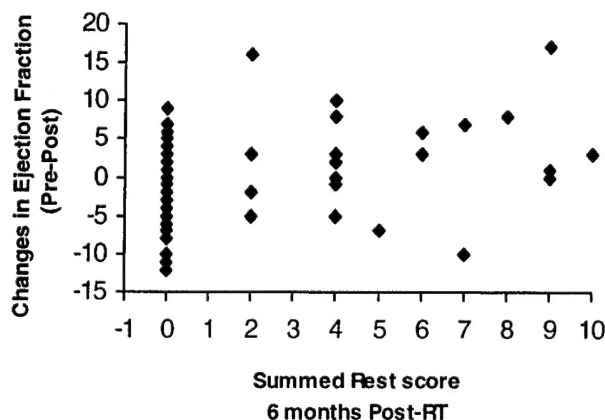
## 2) 3-year effect of chemotherapy and race

**Chemotherapy Impact:** 67% (85/126) of the patients enrolled in the protocol thus far have received chemotherapy prior to radiation. Chemotherapy was Dox-based in 60% of these patients. Although treatment with chemotherapy is significantly correlated with the development of perfusion defects following RT on univariable analysis, our preliminary analysis suggests that this association is confounded by a more important variable, namely the volume of heart irradiated. Patients who received the chemotherapy typically had larger volumes of the left ventricle irradiated. We are currently performing a multivariable analysis to determine if chemotherapy affects the incidence/severity of RT-induced cardiac perfusion defects, after controlling for irradiated volume. We will continue to enroll patients in order to add statistical power to the multivariable analysis.

**Race Impact:** The number of AA patients enrolled in the study to date is too small and the duration of FU too short to permit meaningful analysis of the impact of race on cardiac function following RT. We will continue to enroll additional AA patients and follow currently enrolled patients over the coming year in order to gather enough data for analysis.

## 3) changes in regional and global function

To date, we have not seen any consistent association between the presence of a new RT-induced perfusion defects and clinically significant changes in cardiac ejection fraction. The relationship between these two variables in 72 patients analyzable at the 6 month FU endpoint is shown in **Figure 4**. Our data indicates that more decline in ejection fraction (EF) correlates with the extent of perfusion defect (as measured by the SRS score). We will continue to study this issue.



**h. If appropriate, submit paper for publication based on 3-year data.**

Three-year data were presented orally at the 44th Annual American Society for Therapeutic Radiology and Oncology Meeting (New Orleans, October 2003). A manuscript based on these data is in preparation.

**Difficulties in Accomplishing Tasks:**

We were unable to accrue patients to this study from January, 2002 until January, 2003 while the protocol was re-submitted to the DOD and Duke University Institutional Review Board (IRB) for approval.

**Recommended Changes or Future Work:**

In future work, consideration will be given to using additional imaging modalities to measure changes in cardiac perfusion, wall motion, and ejection fraction. Two promising cardiac imaging modalities are magnetic resonance imaging (MRI) and positron emission tomography (PET). We anticipate



considering using serial MRI to measure changes in regional microvascular cardiac perfusion (similar to what is provided by SPECT). We also hope to perform MRI-based assessments of regional inflammation, metabolic activity, and coronary artery blood flow. We anticipate using serial PET scans to measure regional metabolism in the heart. Images from either MRI or PET scans could be fused to the 3D radiation dose distribution with minor modifications to the image fusion software we currently use to map the SPECT scan data onto the 3D dose distribution.

Changes in physiologic cardiac parameters (perfusion, wall motion, ejection fraction) may be associated with the development of cardiac symptoms or events. We have performed a preliminary analysis to address this question over the past year (Yu et al, San Antonio Breast Cancer Symposium, 2002). We plan to follow patients carefully in the coming years to monitor for cardiac symptoms and report our findings with longer FU.

Given the findings of persistent perfusion defects post-RT, we have been further evaluating methods to reduce the incidental cardiac exposure which occurs during RT for breast cancer. We have quantitatively studied the impact of placing a heart block in conventional tangent fields on the coverage of breast tissue (Quarranta et al, San Antonio Breast Cancer Symposium, 2002).

#### **KEY RESEARCH ACCOMPLISHMENTS:**

- We have recruited 5 additional African American patients to help determine if race is an independent predictor of cardiac injury following left sided radiation for breast cancer.
- We have established the first dose-response curves for RT-induced perfusion defects in the heart in a group of patients analyzed at 6, 12, 18, and 24 months following RT.
- We have enrolled a total of 127 patients on the protocol. We have performed additional scans at 6, 12, 18, and 24 months post-RT. In addition we have performed the first-ever FU SPECT scans at 36 and 48 months in a small group of patients and demonstrated that the presently identified perfusion defects are largely persistent.
- With additional FU, we have further characterized the relationships between radiation dose/volume and cardiac perfusion changes, between perfusion changes and changes in cardiac wall motion, between changes in wall motion and changes in ejection fraction.
- We have investigated whether changes in the physiologic cardiac parameters listed above are associated with development of cardiac symptoms or events.
- We have shown an association between perfusion defects and wall motion changes.

**REPORTABLE OUTCOMES:****Manuscripts and Abstracts:**

Munley MT, Marks LB, Hardenbergh PH, Bentel GC: Functional imaging of normal tissues with nuclear medicine: Applications in radiotherapy. *Seminars in Radiation Oncology* 11(1):28-36, 2001.

Marks LB, Bentel GC, Hardenbergh PH, Lind PAR, Prosnitz LR. A practical and easy method to locate the first three internal mammary lymph-node bearing areas. *Int. J. Radiat. Oncol. Biol. Phys.* 50(2):421-425, 2001.

Hardenbergh PH, Munley MT, Bentel GC, Kedem RR, Borges-Neto S, Hollis D, Prosnitz LR, Marks LB. Cardiac Perfusion Changes in Patients Treated for Breast Cancer with Radiation Therapy and Doxorubicin: Preliminary Results. *Int. J. Radiat. Oncol. Biol. Phys.* 49:1023-1028, 2001.

Hardenbergh PH, Munley MT, Bentel GC, Strickland J, Borges-Neto S, Hollis D, Prosnitz LR, Marks LB: Pathophysiologic impact of doxorubicin (Dox) and radiation therapy (RT) on the heart of patients treated for breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 45(3) (Suppl):197, 1999.

Hardenbergh PH, Munley MT, Hu CY, Borges-Neto S, Hollis DR, Marks LB: Breast cancer treatment related myocardial damage appears increased in African-American Women. Proceedings of ASCO 2001, 20 (1 of 2):29a, 2001.

Lind PA, Pagnanelli R, Marks LB, Hu C, Borges-Neto S, Hardenbergh PH. Myocardial perfusion changes in patients treated with left-sided breast cancer and correlation with coronary artery distribution. Proceedings of the 43rd American Society of Therapeutic Radiology and Oncology Annual Meeting. *Int. J. Radiat. Oncol. Biol. Phys.* 5(suppl 1):157-158, 2001.

Hardenbergh P, Munley M, Hu C, Hollis D, Light K., Blazing M, Borges-Neto S, Marks L. Doxorubicin-based chemotherapy and radiation increase cardiac perfusion changes in patients treated with left-sided breast cancer. Proceedings of ASTRO. *Int. J. Radiat. Oncol. Biol. Phys.* 5(suppl 1):158, 2001.

Yu XL, Prosnitz R, Zhou SM, Hardenbergh P, Tisch A, Blazing M, Borges-Neto S, Hollis D, Wong T and Marks L. Symptomatic "cardiac" events following radiation therapy (RT) for left-sided breast cancer: possible association with RT-induced changes in regional perfusion. *Breast Cancer Research and Treatment*. 2002; 76(suppl. 1), #464.

Prosnitz R, Zhou SM, Yu XL, Hardenbergh P, Tisch A, Blazing M, Borges-Neto S, Wong T and Marks L. Long term radiation (RT)-induced cardiac perfusion

defects following left sided tangential breast-chest wall irradiation. *Breast Cancer Research and Treatment* 2002; 76 (suppl. 1), #457.

Quarranta BP, Prosnitz, R, Light KL, Steffey B, Hardenbergh P, Marks LB. Customized blocking of tangential radiation (RT) breast fields: excluding the heart vs. covering the breast. Striking a balance. *Breast Cancer Research and Treatment* 2002; 76 (suppl. 1), #460.

Marks L, Prosnitz R, Zhou SM, Yu XL, Hardenbergh P, Tisch A, Blazing M, Hollis D, Borges-Neto S, Wong T and Marks L. Functional Consequences of Radiation (RT)-induced Perfusion Changes in Patients with Left-Sided Breast Cancer. Proceedings of ASTRO, Oct 2002; 54, #1.

Xiaoli Yu, M.D., Robert R. Prosnitz, M.D., Sumin Zhou, Ph.D., Patricia H. Hardenbergh, M.D., Andrea Tisch, B.A., Michael A. Blazing, M.D., Salvador Borges-Neto, M.D., Donna Hollis, M.S., Terrance Wong, M.D., Lawrence B. Marks, M.D. Symptomatic "Cardiac" Events Following Radiation Therapy (RT) for Left-sided Breast Cancer: Possible Association with RT-induced Changes in Regional Perfusion. *Clinical Breast Cancer (in press 2003)*.

Marks, Lawrence Bruce; Yu, Xiaoli ; Zhou, Su-Min ; Prosnitz, Robert G; Hardenbergh, Patricia ; Hollis, Donna ; Blazing, Michael; Wong, Terrence ; Coleman, Edward ; Tisch, Andrea ; Borges-Neto, Salvatore . The impact of irradiated left ventricular volume on the incidence of radiation-induced cardiac perfusion changes. Accepted for oral presentation at the 45<sup>th</sup> Annual Meeting of ASTRO, Salt Lake City, Utah, Oct 2003.

## **CONCLUSIONS:**

### **Clinical Relevance:**

- RT-induced cardiac injury appears to be common in patients with breast cancer receiving left-sided RT.
- Treatment of left-sided breast cancer may be effected by the results of this study. The development of 3-D treatment planning to limit treatment-induced heart damage may become more widely applied.
- A better understanding of RT-induced cardiac dysfunction (with or without chemotherapy) may help us better plan therapies for women with breast cancer.
- While this study addressed only patients with breast cancer, its findings are applicable to patients with other diseases as well. Recognition of RT-induced cardiac dysfunction, and its dose/volume-dependence, may impact on

therapy for patients with cancers of the lung, esophagus, mediastinal tissues and upper abdomen.

**Conclusions:**

RT induces dose-dependent changes in regional cardiac perfusion within the region of heart irradiated. This suggests that RT may cause microvascular damage to the heart. To date, there have been no clinically-relevant cardio-toxic events observed, and thus the clinical importance of these perfusion changes remains unclear. However, these perfusion abnormalities are associated with wall motion defects. The incidence of these perfusion defects appears higher in patients who also receive chemotherapy (vs. RT alone) and in African Americans (vs. Caucasians). Additional follow-up of the current cohort of patients, plus the study of additional patients, will help determine if these perfusion defects are persistent, if they have long-term clinical significance, and the role of chemotherapy and race in their evolution.

**Personnel:**

Lawrence Marks, Robert G. Prosnitz, Salvador Borges-Neto, Michael Blazing, Su-Min Zhou, Donna Hollis, Xiaoli Yu, Andrea Tisch